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Synthesis of chiral piperazin-2-ones through palladium-catalyzed asymmetric hydrogenation of pyrazin-2-ols†

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A palladium-catalyzed asymmetric hydrogenation of pyrazines containing a tautomeric hydroxyl group has been developed, providing a facile access to chiral disubstituted piperazin-2-ones with excellent diastereoselectivities and enantioselectivities. The product could be conveniently converted into chiral piperazines without loss of optical purity.

The piperazin-2-one motif is becoming increasingly popular in small-molecule drugs and bioactive natural products, and well regarded as a privileged scaffold in medicinal chemistry.[1] Representative examples include praziquantel (**I:** a well-known antihelminthic drug),[2] (−)-agelastatin A (**II:** a potent anticancer alkaloid),[3] piperazirum (**III:** a new alkaloid with significant anticancer activity)[4] and pseudotheonamide A_1 (**IV:** a serine protease inhibitor, Fig. 1).[5] Additionally, piperazin-2-ones can also play a central role in conformationally constrained peptides for the discovery of bioactive peptidomimetic drugs.[1b,6]

Although there is a large demand of chiral piperazin-2-ones for medicinal chemistry investigation, the current protocols for this kind of motif exclusively rely on classical "chiral pool" techniques, such as the use of amino acid derivatives as starting materials[1a,7] and chiral-auxiliary-promoted dynamic resolutions[8] or alkylations.[9] The synthesis of chiral piperazin-2-ones in an asymmetric catalytic manner is particularly challenging. To date, few examples have been reported. For example, the Bode group developed a kinetic resolution of N-heterocycles through catalytic *N*-acylation employing the combination of a chiral hydroxamic acid catalyst and an achiral N-heterocyclic carbene.[10] The substrate scope could be expanded to piperazinones *via* improving the reaction conditions and catalysts.[10b] In 2015, Stoltz and co-workers reported an elegant palladium-catalyzed asymmetric allylic alkylation approach for the synthesis of chiral piperazin-2-ones (Scheme 1).[11] Recently, Zhang *et al.* have successfully developed an iridium-catalyzed asymmetric hydrogenation of unsaturated piperazin-2-ones, affording chiral piperazin-2-ones with good enantioselectivities.[12] Furthermore, some expedient approaches were also applied to furnish this important motif *via* cyclization of the key chiral intermediates and diamines. The Fox group identified a Ru-catalyzed enantioselective transfer hydrogenation of trichloromethyl ketones. The resulting products of α-trichloromethylalcohols were transformed into enantiomerically enriched piperazin-2-ones by the subsequent Jocic-type reactions.[13] Lattanzi's group realized a simple one-pot protocol to prepare chiral piperazin-2-ones, which features organocatalytic asymmetric epoxidation of alkylidenemalononitriles as the key step.[14] Subsequently, Kokotos' group developed a four-step synthesis reaction for converting simple aldehydes into chiral piperazin-2-ones.[15] However, the above studies mainly focus on α-substituted chiral piperazin-2-ones. Thus, the development of a method that allows for the direct construction of piperazin-2-one derivatives with structural

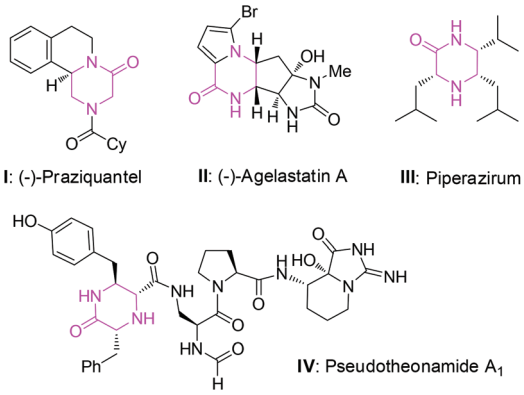

Fig. 1 Bioactive molecules containing the piperazin-2-one motif.

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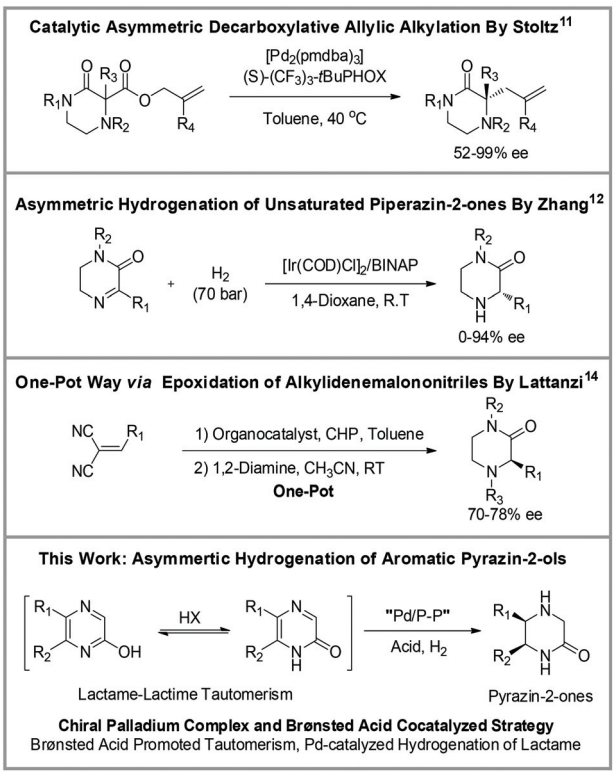


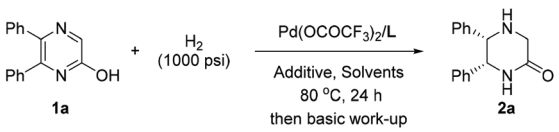
Scheme 1 Enantioselective synthesis of chiral piperazin-2-ones.

diversity for medicinal chemistry research and new drug discovery remains highly desirable and valuable.

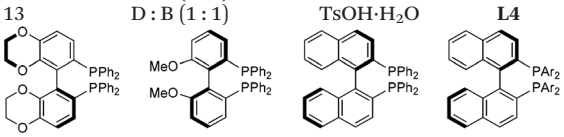
On examining the retrosynthetic analysis, it is observed that asymmetric hydrogenation of pyrazines allows for direct access to chiral piperazines. Although asymmetric hydrogenation of N-heteroaromatics has been well developed as an effective method to furnish chiral N-heterocycles in the past years,[16] pyrazine remains an unresolved substrate class that is plagued by notably high stability and the poisoning effects of two pyridine-like nitrogens towards metal catalysts. So far, only a few homogeneous rhodium and iridium catalysts have been applied to asymmetric hydrogenation of some special pyrazines or pyrazinium salts.[17] Very recently, our group proposed a transformation that would allow for a facile access to chiral cyclic ureas through asymmetric hydrogenation of pyrimidines containing a tautomeric hydroxyl group. The key to success in this case was the hydroxyl-oxo tautomerism of 2-hydroxypyrimidine causing a certain loss of aromaticity.[18] This result showed us a new strategy of asymmetric dearomatization of N-heteroaromatics. Inspired by this pioneering research, we envisioned that the asymmetric hydrogenation of aromatic pyrazin-2-ol could directly construct the important chiral piperazin-2-one skeleton. Herein, we report a novel methodology for the synthesis of chiral piperazin-2-ones *via* palladium-catalyzed asymmetric hydrogenation of pyrazin-2-ols, affording chiral 5,6-disubstituted piperazin-2-ones with high yields and stereoselectivities.

At the outset of our study, 5,6-diphenylpyrazin-2-ol (**1a**) was selected as the model substrate. Asymmetric hydrogenation was conducted in the presence of *p*-toluenesulfonic acid monohydrate ($TsOH{\cdot}H_2O$) in 2,2,2-trifluoroethanol (TFE) with $Pd(OCOCF_3)_2$/(*S*)-synphos (**L1**) as the chiral catalyst, affording the desired product with >95% conversion, 42% ee and greater than 20 : 1 diastereoselectivity (Table 1, entry 1). Initially, solvent effects were examined (entries 1–6). It was noted that a 1 : 1 (v/v) mixture of DCM/benzene was the best choice with respect to the conversion, diastereoselectivity and enantioselectivity (>95% conversion, >20 : 1 dr and 82% ee, entry 4). Subsequently, the effect of the Brønsted acid on the enantioselectivity and reactivity was investigated (entries 7–10). As expected, the Brønsted acid was neccessary in this asymmetric hydrogenation system (entry 7). When either L-camphorsulfonic acid or D-camphorsulfonic acid was used, the reaction proceeded well and with almost the same enantioselectivity. These results reflected that the chirality of the additive had no obvious influence on the stereoselectivity of the hydrogenation (entries 8 and 9). Trifluoroacetic acid (TFA) also provided the desired product, but unfortunately with much lower enantioselectivity (entry 10). Lastly, we further probed the influence of chiral ligands (entries 11–13). When using the electron-rich bisphosphine ligand (*R*)-TolBINAP (**L4**), the best

Table 1 Optimization of reaction conditions[a]



Entry	Solvents	Additive	L	Ee[b] (%)
1	TFE	$TsOH{\cdot}H_2O$	**L1**	42 (*R*,*S*)
2	Benzene (B)	$TsOH{\cdot}H_2O$	**L1**	77 (*R*,*S*)
3	DCM (D)	$TsOH{\cdot}H_2O$	**L1**	71 (*R*,*S*)
4	D : B (1 : 1)	$TsOH{\cdot}H_2O$	**L1**	82 (*R*,*S*)
5	D : B (1 : 2)	$TsOH{\cdot}H_2O$	**L1**	81 (*R*,*S*)
6	D : B (2 : 1)	$TsOH{\cdot}H_2O$	**L1**	80 (*R*,*S*)
7[c]	D : B (1 : 1)	—	**L1**	—
8	D : B (1 : 1)	L-CSA	**L1**	81 (*R*,*S*)
9	D : B (1 : 1)	D-CSA	**L1**	82 (*R*,*S*)
10	D : B (1 : 1)	TFA	**L1**	66 (*R*,*S*)
11	D : B (1 : 1)	$TsOH{\cdot}H_2O$	**L2**	86 (*S*,*R*)
12	D : B (1 : 1)	$TsOH{\cdot}H_2O$	**L3**	89 (*S*,*R*)
13	D : B (1 : 1)	$TsOH{\cdot}H_2O$	**L4**	90 (*S*,*R*)



L1: (*S*)-SynPhos **L2**: (*R*)-MeOBiPhep **L3**: (*R*)-BINAP **L4**: (*R*)-TolBINAP

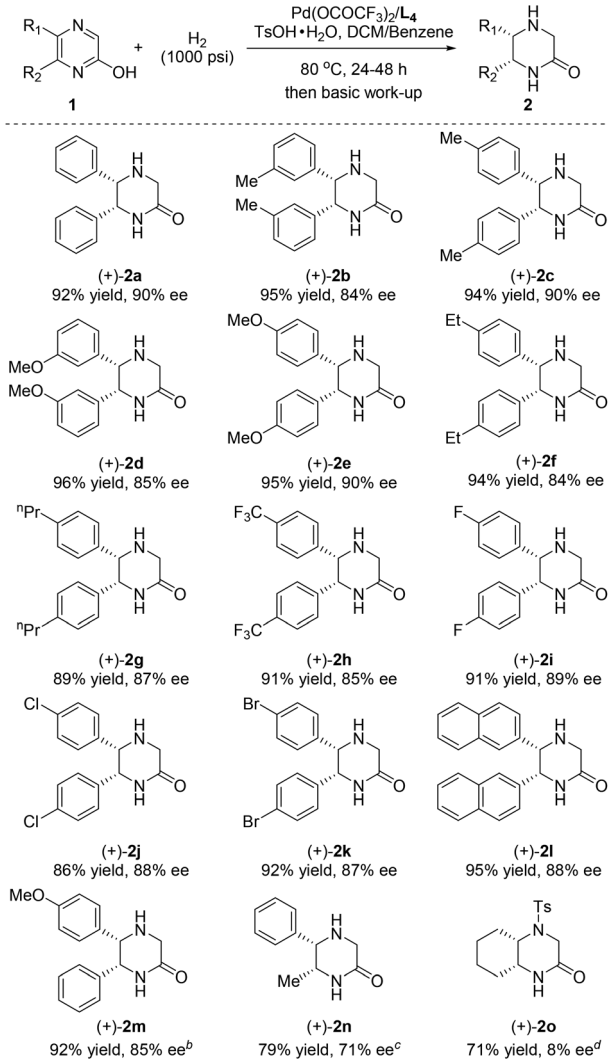
[a] Reaction conditions: **1a** (0.2 mmol), $Pd(OCOCF_3)_2$ (3.0 mol%) and **L** (3.3 mol%), additive (100 mol%), solvents (3 mL), H_2 (1000 psi), 80 °C, 24 h. Reaction conversion and dr were determined by ^1H NMR spectroscopy, if not noted, conversion >95%, dr > 20 : 1. [b] Determined by HPLC using a chiral stationary phase. [c] Conversion <5%. L-CSA: L-camphorsulfonic acid. D-CSA: D-camphorsulfonic acid. $TsOH{\cdot}H_2O$: *p*-toluenesulfonic acid monohydrate. TFA: trifluoroacetic acid. TFE: 2,2,2-trifluroroethanol. DCM: dichloromethane.

enantioselectivity and diastereoselectivity were obtained (90% ee and >20 : 1 dr, entry 13). Therefore, the optimized conditions were established as follows: $Pd(OCOCF_3)_2$/(*R*)-TolBINAP, $TsOH{\cdot}H_2O$ (100 mol%), H_2 (1000 psi), dichloromethane/benzene (1 : 1), 80 °C.

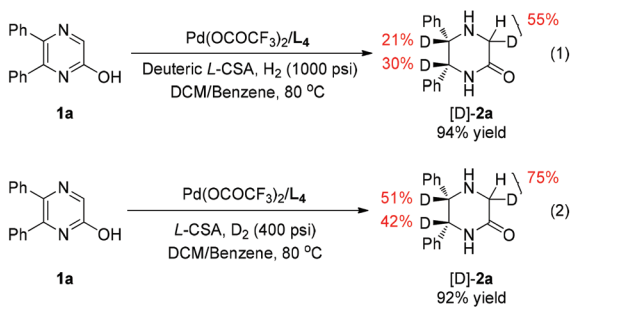
In order to probe the generality of the catalytic system, a series of 5,6-disubstituted pyrazin-2-ols were subjected to hydrogenation under the optimized conditions, and the results are presented in Scheme 2. As expected, a variety of 5,6-disubstituted pyrazin-2-ols were smoothly converted into piperazin-2-ones with high yields and 84–90% ee (Scheme 2, **2a–2l**). It was noteworthy that the electronic properties and position of substituents on the aromatic ring had a prominent effect on the enantioselectivities. For example, the ee values slightly decreased when the substituents were at the 3-position of aryl rings (**2b**), in contrast to the analogous 4-substituted product (**2c**). Meanwhile, the substrates with more electron-donating groups such as methoxy gave near-identical results (**2d** and **2e**). For other alkyl substrates, the reaction proceeded smoothly, giving the target product with good yields and enantioselectivities (**2f–2g**). Compared with the results of electron-donating groups, the substrate with the electron-withdrawing group $-CF_3$ gave the product with 95% yield and 85% ee (**2h**). In addition, the substrates with halides afforded the corresponding products with good yields and 87–89% ee (**2i–2k**). The 2-naphthyl substrate also underwent the reduction smoothly, delivering the product with 95% yield and 88% ee (**2l**). Moving forward, various aryl disubstituted substrates were also investigated.[19] For example, the substrate **1m** was well compatible in this system, giving the desired product in a good yield (**2m**).[20] The substrate with alkyl and aryl substituents was also examined (**1n**), and the corresponding product was obtained with an acceptable yield and enantioselectivity. Finally, the alkyl-disubstituted cyclic substrate also produced the product with 71% yield and 8% ee value (**2o**). Notably, low reactivity was observed for monosubstituted pyrazin-2-ols, which might be ascribed to the strong coordinative ability of N atoms of the substrate and the reductive product.

To investigate the process of the reaction, two isotopic labelling experiments were carried out (Scheme 3). The hydrogenation of **1a** was performed in deuterium acid, and the distribution of deuterium in the deuterated product ([D]-**2a**) revealed that 55%, 21%, and 30% of deuterium was incorporated at the C-3, C-5, and C-6 positions, respectively. When **1a** was subjected to hydrogenation with D_2, 75%, 51% and 42% of deuterium atoms were incorporated at the C-3, C-5, and C-6 positions, respectively. These results suggested that the hydrogenation of **1a** mainly proceeded *via* piperazin-2-one intermediates in the presence of an acid, and the tautomerization process of enamine to imine intermediates was faster than the hydrogenation, which may involve a dynamic kinetic resolution process.

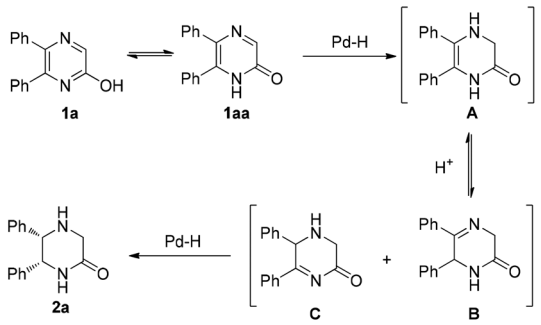
Based on above the experimental data, a stepwise hydrogenation process was proposed (Scheme 4). Firstly, an initial reduction at the C(3)=N(4) bond in piperazin-2-one gives 3,4-dihydropyrazin-2(1*H*) intermediate **A**. In the presence of a Brønsted acid, the left side enamine is prone to isomerization



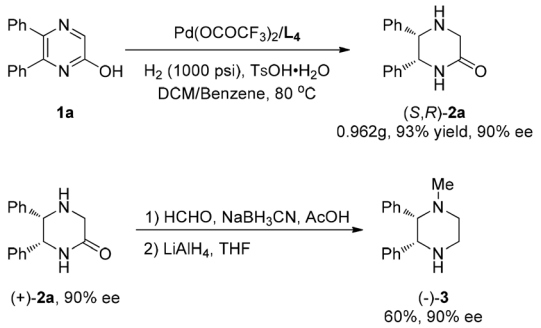
Scheme 2 The substrate scope of 5,6-disubstituted pyrazin-2-ols [a]Reaction conditions: **1** (0.3 mmol), $Pd(OCOCF_3)_2$ (3.0 mol%) and (*R*)-TolBINAP (3.3 mol%), $TsOH{\cdot}H_2O$ (100 mol%), DCM/benzene (1.5 mL/1.5 mL), H_2 (1000 psi), 80 °C, 24 h. dr was determined by ^1H NMR spectroscopy. If not noted, dr > 20 : 1. [b]48 h. [c]dr = 9.5 : 1. [d]The yield of the Ts-protected product, 48 h.



Scheme 3 Mechanistic investigation.



Scheme 4 Proposed reaction pathway.



Scheme 5 Gram-scale reaction and product elaboration.

between 1,6-dihydropyrazin-2(3*H*)-one **B** and 4,5-dihydropyrazin-2(3*H*)-one **C**. Asymmetric hydrogenation of two imines delivers chiral piperazin-2-ones. Indeed, a dynamic kinetic resolution process is involved in this formal asymmetric hydrogenation reaction.

To demonstrate the practical utility of our methodology, the asymmetric hydrogenation of **1a** was performed at the gram scale to give the desired product **2a** with 93% yield and 90% ee without loss of reactivity and enantioselectivity (Scheme 5). Meanwhile, the methylation of **2a** was performed through treatment with formaldehyde through reductive amination. The product was then reduced by $LiAlH_4$, providing the chiral piperazine with maintained optical purity.

Conclusions

In summary, a palladium-catalyzed asymmetric hydrogenation of aromatic pyrazin-2-ols has been developed for the efficient synthesis of chiral piperazin-2-ones with up to 90% ee. In addition, preliminary mechanistic studies shed some light on the reaction pathway. The practicality of the reaction was demonstrated by the easy scalability and synthesis of chiral piperazines. Further efforts to apply the developed method to other related challenging heteroaromatics are ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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20 The position of the hydroxyl group is confirmed by single crystal diffraction. The CCDC number is 2023354.†